HYPERPROLACTINAEMIA IN THE SPONTANEOUSLY HYPERTENSIVE RAT

By

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ABSTRACT

A hypothalamic role in the aetiology of hypertension in the spontaneously hypertensive rat (SHR) has been suggested by prior observations. In an attempt to determine whether the central control of prolactin (PRL) release is altered in the SHR we have compared the PRL response to immobilization stress, thyrotrophin releasing hormone (TRH), haloperidol, and L-DOPA in the SHR and in normotensive Wistar control rats. Carotid artery catheters were inserted 48 h prior to the PRL response studies and the catheters were maintained patent with heparinized saline. Timed blood samples were obtained in SHR and control rats weighing 180–225 g. The SHR demonstrated elevated basal serum levels of PRL and greater PRL responses to stress. However, administration of L-DOPA resulted in a similar suppression of serum PRL in the SHR and in the normotensive controls. These findings suggest alteration in the central control of PRL release in the SHR. Observations of elevated basal PRL, exaggerated PRL in response to L-DOPA in SHR are consistent with normal pituitary responsiveness to dopamine suppression of PRL release, but defective hypothalamic metabolism of dopamine. Alterations in central dopamine control mechanisms in the SHR may play a role in the pathogenesis of essential hypertension in these animals.

A strain of spontaneously hypertensive rats (SHR) was isolated from Wistar rats (Okamoto 1969) and observed to have larger pituitaries, adrenals, and thyroids. In the SHR blood pressure rises progressively with age, and vascular lesions of the heart, brain, and kidney are similar to those found in patients with essential hypertension (Okamoto 1969). These observations suggest that SHR is an excellent experimental model for studying the aetiology of essen-
tial hypertension (Julius et al. 1971), the young SHR responds to environmental stimuli with exaggerated heart rate and blood pressure rises that are primarily central in origin (Hallback & Folkow 1974). It has been suggested (Folkow & Rubinstein 1966) that the cardio-vascular system of the SHR is exposed to an increased neuro-hormonal discharge as a result of exaggerated hypothalamic defense area activity. A hypothalamic role in the aetiology of hypertension in the SHR is further suggested by the observations that these animals display signs of an intensified activity not only of the sympathicoadrenal system, but also of the ACTH-corticoid and TSH-thyroid systems (Okamoto 1969; Tabei et al. 1972). Recently (Stumpe et al. 1977) reported that a group of patients with mild essential hypertension had elevated serum prolactin (PRL) levels. Treatment with bromocriptine affected a substantial reduction in blood pressure which correlated well with the fall in their PRL levels. The results of that study suggest that the role of PRL in the aetiology of essential hypertension needs further exploration. In this investigation we have examined the PRL response to immobilization stress, thyrotrophin releasing hormone (TRH), haloperidol, and L-DOPA in the SHR and normotensive control Wistar rats to determine if alterations occur in the central control of PRL release in the SHR.

**Materials and Methods**

Twenty male SHR and 20 male normotensive Wistar-Kyoto rats, weighing 180–225 g were individually caged and maintained at 23°C on a light dark cycle of 14:10. The animals were fed and watered *ad libitum*. A 25 cm polyethylene catheter (PE 50) was inserted through the right common carotid artery under Nembutal anaesthesia as previously described (Popovic & Popovic 1960). The catheters were passed subcutaneously, exteriorized, and coiled immediately posterior to the shoulders. Catheters were filled with heparinized saline (200 USP units/ml) and sealed with heat. Catheters were maintained patent by flushing with 200 USP units heparin daily. Blood was drawn through a 23-gauge needle inserted into the end of the catheter 48 h after surgery. All blood samples were 400 μl in volume and an equal volume of the normal saline was replaced when each blood sample was taken. Mean arterial blood pressure was monitored from the same cannula using a physiograph pressure transducer and recorder.

Five SHR and 5 normotensive Wistar control rats were studied. The catheter was uncoiled and passed through the top of a restraining cage, after which the animal was left undisturbed for 60 min before baseline samples were obtained. The rats were then immobilized in a prone position for 3 h by inserting their heads through steel wire loops fixed on a plate and by fastening their limbs with adhesive tape. Blood samples were withdrawn through the catheter at 1, 2 and 3 h after onset of immobilization.

Five SHR and five control rats had baseline samples withdrawn 60 min after their catheter was uncoiled and passed through the top of the cage. TRH (10 μg/kg) was injected through the catheter and samples of blood were withdrawn at 10, 15, 30 and 45 min after TRH injection.

Haloperidol (0.5 mg/kg) was given ip and blood samples were withdrawn at 0, 30, 45 and 60 min in 5 SHR and 5 control rats.
Table 1.
Mean (± sem) serum PRL (ng/ml) response to immobilization stress in 5 spontaneously hypertensive rats (SHR) and 5 normotensive Wistar control rats.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>60 min</th>
<th>120 min</th>
<th>180 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR</td>
<td>33.8 ± 4.7</td>
<td>56.5 ± 10.2</td>
<td>68.0 ± 15.9</td>
<td>73.7 ± 17.8</td>
</tr>
<tr>
<td>Controls</td>
<td>20.4 ± 4.7</td>
<td>34.0 ± 10.8</td>
<td>33.0 ± 11.8</td>
<td>42.2 ± 15.0</td>
</tr>
</tbody>
</table>

Baseline blood samples were withdrawn and L-DOPA (50 mg/kg) was injected in 5 SHR and 5 controls. Blood samples were taken at 45, 60 and 90 min after L-DOPA injection.

PRL was measured by a double antibody radioimmunoassay using materials provided by the NIAMDD. NIH PRL RP-1 served as the reference preparation. All serum PRL

Fig. 1.
Mean serum PRL responses to TRH (given at 0 time) in 5 spontaneously hypertensive rats (solid line) and in 5 normotensive Wistar-Kyoto rats (broken line); vertical bars show SEM.
Mean serum PRL responses to haloperidol (given at 0 time) in 5 spontaneously hypertensive rats (solid line) and in 5 normotensive Wistar-Kyoto rats (broken line); vertical bars show SEM.

measurements expressed in ng/ml of the reference were performed in duplicate in the same assay to avoid inter-assay variation. Statistical differences between the PRL responses of the SHR and the control groups were examined using a Mann Whitney non-parametric U-test.

RESULTS

Table 1 shows that mean baseline serum PRL levels were higher \( (P < 0.05) \) for the SHR group \( (33.8 \pm 4.7 \text{ ng/ml}) \) than for the Wistar control group \( (20.4 \pm 3.5 \text{ ng/ml}) \). The mean serum PRL (stimulated-baseline) response to immobilization in the SHR group was greater \( (P < 0.05) \) at 60, 120 and 180 min than for the control group. The max\( \Delta \)PRL (peak-baseline) response to immobilization was greater \( (P < 0.025) \) for the SHR group \( (40.1 \pm 9.4 \text{ ng/ml}) \) than for the controls \( (21.4 \pm 6.7 \text{ ng/ml}) \).

Fig. 1 demonstrates that in rats receiving TRH the mean serum basal PRL level was higher \( (P < 0.05) \) for the SHR group \( (26.1 \pm 2.1 \text{ ng/ml}) \) than for the
Wistar controls (16.2 ± 1.9 ng/ml). However, when the PRL response at each sampling interval was expressed as per cent change from baseline values there was no significant difference ($P < 0.05$) in the PRL response to TRH for the two groups.

Fig. 2 shows that in the rats receiving haloperidol the mean basal serum PRL for the SHR group (33.1 ± 3.6 ng/ml) was greater ($P < 0.05$) than for the controls (21.7 ± 2.5 ng/ml). The mean serum max.PRL response to haloperidol was similar ($P > 0.05$) for the SHR group (31.7 ± 10.7 ng/ml) and for the control group (27.1 ± 10.6 ng/ml).

Fig. 3 shows that the l-DOPA suppression of mean serum PRL (expressed as per cent of baseline values) was similar ($P > 0.05$) at all sampling times through 90 min in both groups. In the rats receiving l-DOPA the baseline PRL levels were 2.2-fold greater in the SHR group than in the Wistar controls.

The mean arterial blood pressure for the SHR group was 157 ± 20 mmHg and for the Wistar control group 110 ± 7 mmHg.

![Fig. 3](image_url)

Mean serum PRL response to l-DOPA, expressed as per cent of basal values, in 5 spontaneously hypertensive rats (solid line) and in 5 normotensive Wistar-Kyoto rats (broken line); vertical bars show SEM.
DISCUSSION

The results of this study indicate that spontaneously hypertensive rats display elevated basal serum levels of PRL and greater PRL responses to stress. These findings suggest that the central nervous system control of PRL release is altered in the SHR. There is considerable evidence that hypothalamic catecholamines, especially dopamine, suppress PRL secretion (Van Maanen & Smelik 1968; Koch et al. 1970; Shaar & Clements 1974). Dopamine appears to inhibit PRL secretion by stimulation of the release of prolactin inhibiting factor (PIF) from the hypothalamus (Kamberi et al. 1971; Iversen 1975) and probably more importantly by a direct action on the anterior pituitary (Quijada et al. 1974; MacLeod & Lehmeyer 1974).

Thus, high serum basal PRL and exaggerated PRL responses to stress may reflect an alteration of central nervous system function with defective dopamine control. In this study we found that administration of L-DOPA, a precursor of dopamine, resulted in a similar suppression of serum PRL in the SHR and in normotensive Wistar controls. This observation is consistent with normal pituitary responsivity to dopamine suppression of PRL release, but decreased hypothalamic dopaminergic activity. Decreased levels of noradrenaline have been found in the hypothalamus of young SHR (Saavedra et al. 1977); however, no reports of hypothalamic dopamine levels in the SHR are available. Decreased hypothalamic dopaminergic activity could reflect either alteration of synthesis or turnover of dopamine.

Observations from prior studies indicate that central dopamine transmission mechanisms may be involved in blood pressure regulation (Henning & Ruben-son 1970; Watanabe et al. 1974). Altered central dopamine control mechanisms in the pathogenesis of hypertension in the SHR could reflect a direct effect on the central dopaminergic system or an indirect effect via elevation of PRL levels. Consistent with the concept of a role for the central dopaminergic system in blood pressure regulation are the data from previous animal work indicating that the antihypertensive effect of levodopa is associated with an accumulation of catecholamines in the cerebral parenchyma (Henning & Ruben-son 1970) and a decrease in central sympathetic outflow (Watanabe et al. 1974). The possibility that elevated PRL levels may play a role in the pathogenesis of hypertension is suggested by several observations. In vitro studies have shown that PRL potentiates the vasoconstrictive responses of rat vascular smooth muscle to norepinephrine and angiotensin (Manku et al. 1973). Prolactin infusions in rabbits in concentrations comparable to physiological secretion rates increases blood pressure (Horrobin et al. 1973). Although hyperprolactinaemia in the SHR could possibly play a direct role in the pathogenesis of hypertension in these animals, it is more likely a reflection of altered CNS dopamine metabolism.
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REFERENCES


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